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Title

How many stroke patients might be eligible for mechanical thrombectomy?

Authors

Salwa El Tawil, MD

Bharath Cheripelli, MRCP

Xuya Huang, MRCP

Fiona Moreton, MRCP

Dheeraj Kalladka

Niall JJ MacDougal, MD

Ferghal McVerry, MD

Keith W Muir, MD, FRCP

Author Affiliation:

Institute of Neuroscience and Psychology, University of Glasgow

Corresponding Author:

Prof. Keith W Muir

Institute of Neuroscience and Psychology

University of Glasgow, Queen Elizabeth University Hospital, Glasgow, Scotland,

United Kingdom G51 4TF

Tel +44 (0)141 451 5874

Fax:

E-mail: Keith.Muir@gla.ac.uk

Short Title:**Key words:**

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Abstract

Introduction

Recent studies showed improved patient outcomes with endovascular treatment of acute stroke compared to medical care, including IV rtPA, alone. Seven trials have reported results, each using different clinical and imaging criteria for patient selection. We compared eligibility for different trial protocols to estimate the number of patients eligible for treatment.

Patients and Methods:

Patient data were extracted from a single centre database that combined patients recruited to three clinical studies, each obtained both CTA and CTP within 6h of stroke onset. The published inclusion and exclusion criteria of seven intervention trials (MR CLEAN, EXTEND-IA, ESCAPE, SWIFT-PRIME, REVASCAT, THERAPY and THRACE) were applied to determine the proportion that would be eligible for each of these studies.

Results:

A total of 263 patients was included. Eligibility for IAT in individual trials ranged from 53% to 3% of patients; 17% were eligible for 4 trials and under 10% for 2 trials. Only three patients (1%) were eligible for all studies. The most common cause of exclusion was absence of large artery occlusion (LAO) on CTA. When applying simplified criteria requiring and ASPECT score >6, 16% were eligible for IAT, but potentially 40% of these patients were excluded by perfusion criteria and more than half by common NIHSS thresholds.

Conclusion:

Around 15% of patients presenting within 6h of stroke onset were potentially eligible for IAT, but clinical trial eligibility criteria have much more limited overlap than is commonly assumed and only 1% of patients fulfilled criteria for all recent trials.

Introduction:

Between December 2014 and April 2015, five clinical trials were published that showed benefit of intra-arterial therapy (IAT), predominantly using stent-retrievers for thrombectomy, in a subset of acute stroke patients with large artery occlusion (LAO), compared to best medical care (including intravenous recombinant tissue plasminogen activator (IV rtPA) in the majority)¹⁻⁵. Two further trials have presented similar findings^{6, 7}. The success of these trials, compared to previous studies of IAT, was attributed to better patient selection (including the use of advanced imaging), streamlined study procedures to achieve rapid revascularization, and the use of stent retriever devices, capable of producing high rates of recanalization⁸.

Introduction of IAT to routine acute stroke care requires re-organization of stroke services so that patients most likely to benefit are rapidly directed to centres where endovascular services are available. Each of the published or presented IAT trials used different clinical and imaging criteria for patient selection (summarized in table 1). While opinion supports the concept that a common group of readily identifiable patients has been studied in all IAT trials,^{8,9} we hypothesised that if so, then a substantial proportion of patients with acute stroke would be eligible for multiple trial protocols. We tested this by applying trial entry criteria to a database of acute stroke patients, all of whom underwent CT angiography (CTA) and CT perfusion (CTP) in addition to non-contrast CT in the acute stage in order to estimate the number of patients potentially eligible for IAT, and to compare eligibility across different trials.

Patients and Methods:

Patient data were extracted from an acute stroke imaging database that combined patients recruited from three acute studies that acquired multimodal CT less than 6 hours after symptom onset (the multicentre acute stroke imaging study [MASIS],¹⁰ post-stroke hyperglycemia [POSH]¹¹ and Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis [ATTEST]¹² studies) at a single centre between 2008 and 2013. Two studies were observational studies evaluating feasibility of complex imaging and the pathophysiology of hyperglycemia respectively (MASIS and POSH), while the third (ATTEST) compared two different IV thrombolytic agents within 4.5 hours of symptom onset. Entry and exclusion criteria are detailed in supplementary material. Endovascular treatment was not undertaken. Clinical details included demographic and risk factor data, National Institutes of Health Stroke Scale (NIHSS)¹³ scores at onset and 24 hours, estimated pre-morbid modified Rankin Scale (mRS)¹⁴, time from symptom onset to CT and to treatment (if applicable). All patients had non-contrast CT (NCCT), CT perfusion (CTP) and CT angiography (CTA) at presentation. This was performed using a multi-detector Scanner (Philips Brilliance 64 Slice). Whole brain non-contrast CT was acquired first, followed by CT perfusion with 40mm slab coverage (8x5mm slices), using a 50 ml contrast bolus administered at 5mls/second via a large-gauge peripheral venous cannula. Finally a CT angiogram was performed from aortic arch to the top of the lateral ventricles using bolus tracking to enable correct timing of image acquisition.

CTP was processed offline with MiStar (Apollo Medical Imaging Technology, Melbourne, VIC, Australia) to produce Cerebral Blood Flow (CBF) and Cerebral Blood Volume (CBV), Delay Time (DT) and Mean Transient Time (MTT) maps. Ischaemic core was defined as

tissue with reduced CBF (relative CBF <40% of contralesional hemisphere) and prolonged delay time (relative DT >2 sec); penumbra volume was defined as tissue with relative DT >2 sec but relative CBF \geq 40% of contralateral¹⁵. To account for the limited z-axis coverage of CTP, we reduced the 70ml threshold used by EXTEND-IA¹⁶ and DEFUSE-2¹⁷ proportionately. Detailed scan acquisition detailed were previously published¹⁸. We also evaluated baseline NCCT for ASPECT scores¹⁹.

The published inclusion and exclusion criteria of 7 intervention trials (MR-CLEAN¹, EXTEND-IA³, ESCAPE², SWIFT-PRIME^{4, 20}, REVASCAT⁵, THERAPY⁷ and THRACE⁶ were applied to determine eligibility for each study. Minor modifications of inclusion criteria were required to match our data set, as detailed in Supplementary material.

Individual trial criteria were applied to each individual case and eligibility for all possible combinations of trial eligibility were tabulated. We compared patient characteristics of the cases selected from our population with those of each trial. Finally, we calculated the number of patients that would be eligible for IAT in a hypothetical clinical setting using simplified eligibility criteria more reflective of clinical practice.

Results

A total of 263 patients were included (60% male, mean age 70.6yrs). Clinical features in our patients were comparable to those of patients recruited in the published trials, with the exception of a notably lower median NIHSS score on admission compared to trial populations for EXTEND-IA, SWIFT-Prime and REVASCAT, and a longer median onset to IV rtPA administration time (table 2 in supplementary material).

Figure 1 shows the numbers of patients meeting eligibility criteria for each of the seven studies. The widest eligibility criteria identified 53% of patients as potentially eligible for

IAT (for MR CLEAN), declining to 3% for the most restrictive (THERAPY). Figure 2 shows the number of patients eligible for different study combinations, and Figure 3 shows the number of patients excluded by applying the most restrictive inclusion criteria sequentially to our patients. Only 3 patients fulfilled eligibility criteria for all studies. One quarter of the patients excluded based on the narrowest NIHSS range had LAO (Table 1 in Supplementary material). The number of patients excluded based on perfusion or ASPECTS selection varied from 24% to 62%, depending on the site of occlusion and the tissue criteria used (figure 2 in supplementary material).

Figure 4 shows the selection process in a hypothetical clinical setting. Using two simple imaging criteria for patient selection, presence of LAO and ASPECT score >6, 16% of patients would be considered for IAT. The numbers would be reduced further if selection was restricted by onset to treatment time, NIHSS thresholds, or the use of CTP.

Discussion:

Recently published studies have shown that IAT improves outcome in selected patients with large artery occlusive stroke, predominantly as an adjunct to IV rtPA. Since all individual trials were small or modest in size, conducted at highly experienced acute stroke centres, and with somewhat different eligibility criteria, it is important to establish the comparability of populations across different trials, both for data pooling and for service planning. Recent group-level meta-analysis identified significant heterogeneity among published trials ²¹. When applied to a population of acute stroke patients presenting within 6h of symptom onset and with advanced imaging available, but otherwise minimally selected, we found that the number of patients eligible for the different studies individually ranged between 3% and 53%

of all patients in our database, and for all trial protocols except MR CLEAN was <20%. Only 14% would have been eligible for 3 or more of the recent trials.

The most important clinical selection criterion is the NIHSS score, excluding more than 50% of patients when the narrowest range is applied. Previous studies suggested NIHSS score thresholds above 7 - 10 to be associated with higher probability of LAO^{22, 23}. Since any given NIHSS threshold has limited positive predictive value^{24, 25}, however, trials will inevitably arbitrarily restrict recruitment of angiographically appropriate patients by setting NIHSS thresholds. The median NIHSS of patients treated by IAT in published studies was 17, regardless of the pre-specified threshold in protocol inclusion and exclusion criteria. When the same selection criteria were applied to our patients the median NIHSS varied from 11.5 to 16. When applying the clinical selection criteria of MR CLEAN, EXTEND-IA and ESCAPE to our patients, a larger proportion had an M2 occlusion. The lower median NIHSS in our less selected population raises the possibility of additional differences in patient selection processes in published trials that are not evident from trial protocol eligibility alone. The unavailability of trial screening log data for the majority of studies published to date limits our ability to determine whether additional, non-protocol exclusion criteria were applied.

Imaging selection criteria varied among the different studies. Non-invasive imaging of the intracranial circulation, mostly using CTA, was a minimum requirement in all studies. MR CLEAN and THRACE did not specify any additional imaging in patient selection, while all other studies used NCCT criteria to exclude patients with large infarct core. The use of CTP varied: EXTEND-IA used CTP as the major tissue imaging selection method, while its use in SWIFT PRIME, REVASCAT and ESCAPE was variable. It should be noted that CTP was also obtained in a large proportion (66%) of MR CLEAN patients, but was not deployed to influence patient selection or treatment decisions.

About half of our patients were ineligible due to absence of a major vessel occlusion, which is similar to the finding in EXTEND-IA. The number of patients excluded based on additional parenchymal tissue selection criteria in our sample, however, was significantly larger than the 25% reported by the EXTEND IA investigators³, different trial protocols excluding between 36 and 64% of patients with ICA or M1 occlusion. This may be a consequence of the later presentation times in our population, with onset to IV rtPA treatment times of around 180 minutes in our population compared with 85-120 minutes in the trial populations. It is clear that different tissue based selection criteria result in large differences in the population selected, with SWIFT-Prime criteria excluding many more patients than EXTEND-IA criteria. Individual workflow variations make definitive estimates of the impact of different imaging criteria difficult: for example, if NCCT ASPECT score is applied before knowing a CTA result, a different group is excluded compared to applying an ASPECT score to the group with eligible LAO on CTA.

Our study has limitations. We cannot provide a population-based estimate of the proportion eligible, but this was not our goal: rather, we were interested to assess the comparability of the different imaging selection strategies. Our study populations were not highly selected, predominantly including observational data from patients within 6h of symptom onset and applying no exclusions except fitness for follow-up and absence of contraindications to IV contrast administration. The ATTEST trial population (comprising 38% of those included here) required additional eligibility for IV thrombolysis. While our populations closely resembled those reported in the IAT trials, we cannot exclude the possible influence of selection biases in our original study populations influencing the findings. The MR CLEAN trial elected to use wide clinical inclusion criteria, and no formal tissue imaging criteria, and consequently the majority of our patients would have been eligible for this protocol: the

characteristics of our eligible patients correspond closely to the MR CLEAN IAT group, with the exception of longer onset to IV rtPA initiation.

Clinical trial inclusion and exclusion criteria are generally designed to optimise trial efficiency, selecting a responder population in order to maximise the treatment effect size and thus minimise the sample size. Recognising that this inevitably differs from clinical practice, where less restrictive criteria are likely to be employed, we explored a simplified set of selection criteria using only presence of LAO and small core (operationalised as ASPECTS>6), but even in this setting only 16% of patients would be eligible before applying any clinical or tissue selection criteria. Our data do not allow any conclusions about the preferred imaging strategy that would provide the best cost-benefit balance, which will require health economic analyses taking into account key infrastructure available in each region. Such economic analyses should take into consideration the wide variation in requirements for patient transfer and imaging that are implied by our findings.

Conclusion:

In conclusion, it is likely that around 15% of patients presenting within 6h of symptom onset and suitable for imaging selection are potentially eligible for IAT, but additional clinical or imaging selection criteria exclude a widely varying proportion of these patients. The assumption that a common clinical population would be identified despite different trial selection processes does not appear to be supported from our data²⁶, with large differences in those excluded by different criteria, and strikingly only 1% of patients meeting all trial protocols.

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None

Declarations:

Conflicting interest: The authors declare there is no conflict of interest

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Informed consent: Written informed consent was obtained from all subjects before participation in original studies

Ethical approval: Not applicable

Gurantor: K.M.

Contributorship:

K.M. is responsible for study conception and design. S.E.T, B.C., X.H., F.M, DK. N.M and F.M contributed to data collection and analysis. S.E.T, performed statistical analysis and

wrote the first draft. All authors reviewed and edited the manuscript and approved the final version of the manuscript .

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Study	Clinical Criteria				Patients ineligible for IV rtPA	CTA criteria		Tissue Selection Criteria		
	Age	Pre- stroke function	Max Time from onset to endovascular therapy	NIHSS		Extra- cranial ICA occlusion	Occluded arteries	Baseline NCCT	Perfusion Criteria	Collaterals
MRCLEAN¹	≥18	any	6 hours	≥2	No	Included	ICA, M1, M2, A1, A2	Not used for selection	Not used for selection	Not used for selection
ESCAPE²	≥18	Barthel index> 90	12 hours	5>	Included	Included, except for dissection	ICA,M1, M1 Equivalent (two or more M2 occlusions)	ASPECT score> 5	CBV ASPECT score used with different cut off depending on coverage	Collaterals seen in more than 50% of MCA region by multiphase CTA
EXTEND- IA³	≥18	mRS<2	6 hours	any	No	Not included	ICA,, M1 or M2	Hypodensity more than one	Mismatch ratio>1.2	Not used for selection

								third of MCA territory	Absolute mismatch volume>10 Core volume <50 ml	
REVASCAT 5	18- 85	mRS≤1	8 hours	≥6	Included	Included	ICA or M1	ASPECT>6 for patients >80 years ASPECT>9 for patients aged 81-85	CBV ASPECT used in patients treated more than 4.5 hours from symptom onset	Not used for selection
SWIFTPRI ME⁴	18- 80	mRS≤1	6 hours	≥8- <30	No	Not included	ICA or M1	ASPECT>6	Used for some patients only Core volume < 50 ml	Not used for selection

									Total infarct > 100 ml Penumbra volume > 15 ml Mismatch ratio ≥ 1.8	
THRACE⁶	18-80	any	4 hours	≥ 10 - ≤ 25	No	Not included	ICA, M1, upper third of basilar	Not used for selection	Not used for selection	Not used for selection
THERAPY⁷	18-85	mRS=0	Within local thrombolysis window	≥ 8 or aphasic	No	Not included	Large artery occlusion in anterior circulation	Hypodensity more than 1/3 of the MCA territory Clot more than 8mm	Not used for selection	Not used for selection

Table1: Clinical and Imaging inclusion criteria for 7 endovascular treatment trials. ; MRI based imaging criteria not shown.(NIHSS=National Institute of Health Stroke Scale; ICA=Internal Carotid Artery; NCCT=Non Contrast CT; mRS= Modified Rankin Scale; MCA= Middle Cerebral Artery; ASPECT=Alberta Stroke Programme Early CT , CBV=Cerebral Blood volume)

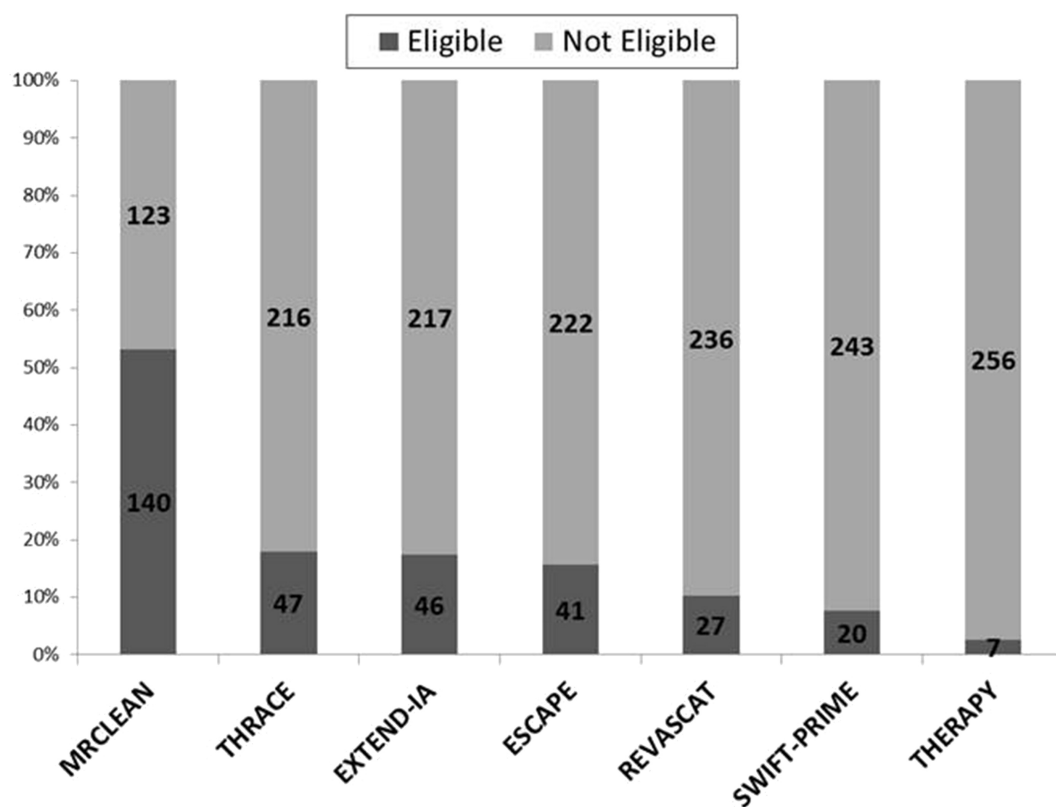


Figure 1. The number of patients meeting entry criteria for each of the studies.

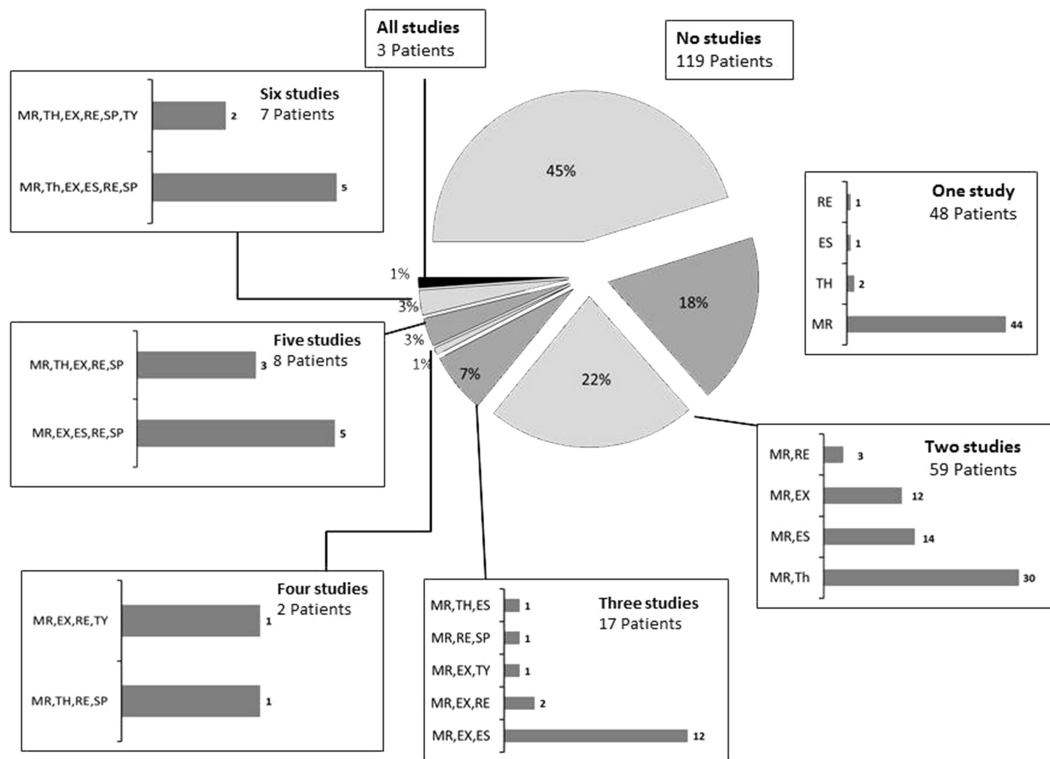


Figure 2. Numbers of patients eligible for different study combinations. MR: MRCLEAN; TH: Thrace; EX: Extend-IA; ES: ESCAPE RE: REVASCAT; SP: SWIFT-PRIME; TY: Therapy.

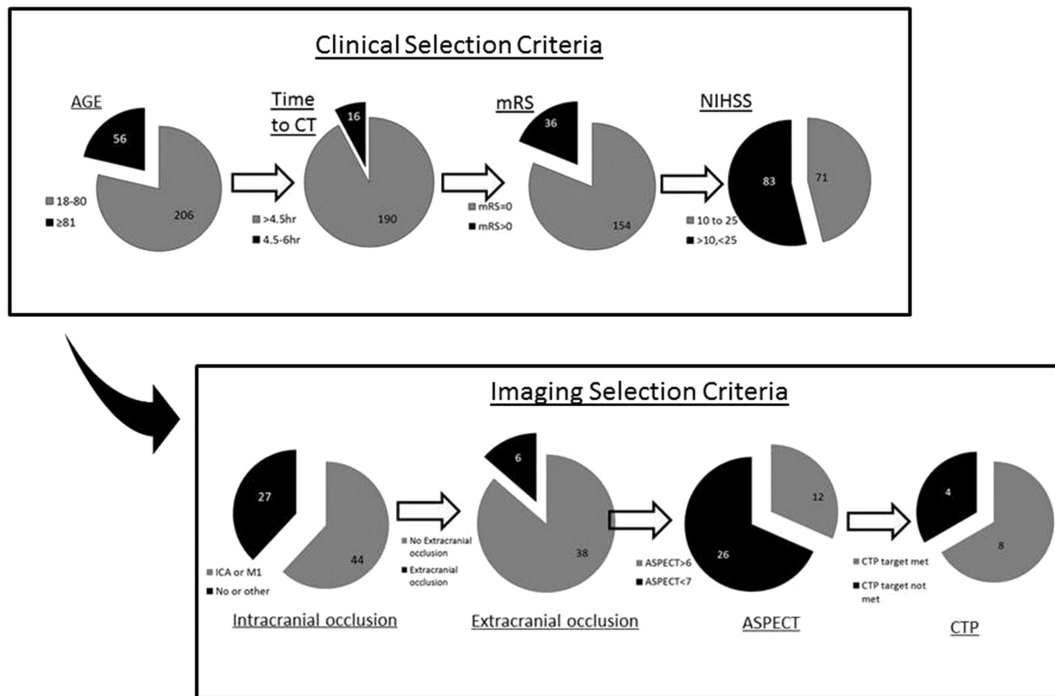


Figure 3. Number eligible to all studies after applying different clinical and imaging selection criteria. The top panel shows sequential exclusion of patients based on clinical criteria, while the bottom panel shows sequential exclusion of patients based on imaging criteria. Of the eight patients meeting CTP target criteria, only three had a visible clot more than 8mm, one of the eligibility criteria of THERAPY trial.

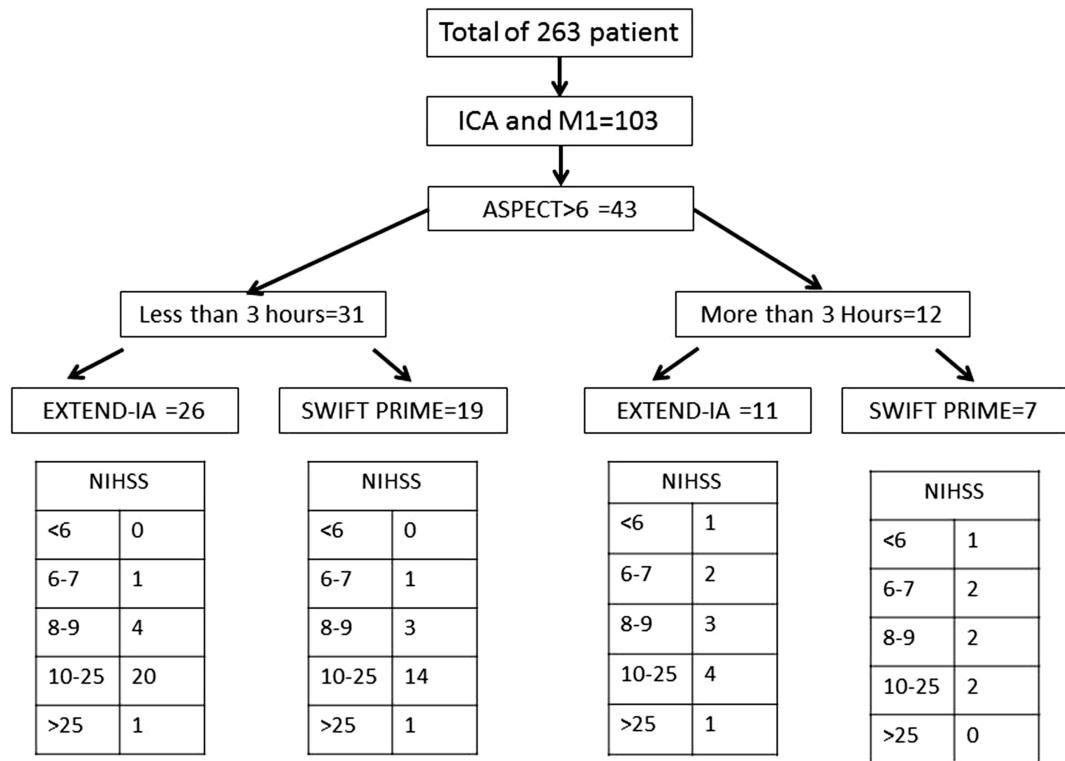


Figure 4. Number of patients with selected for IAT in a hypothetical clinical setting.